bonate (1760 kg). Then, most toluene was evaporated under reduced pressure to a residual amount of about 450 kg. Further removal of toluene and solvent switch to methanol was performed by azeotropic distillation with methanol by repeated (twice) addition of methanol (500 kg) and evaporation of the same amount (500 kg) under reduced pressure. Finally, methanol (830 kg) was added to yield intermediate IV.2 (1280 kg of a 23.6% solution in methanol). Intermediate IV.2 was used as such in the next step.

Synthesis of (IV.4/IV.4') from (IV.2):

Intermediate (IV.2) (503 mol, 520 kg of a 23.6% w/w of IV.2 in methanol) was mixed with nitromethane (1.1 equiv., 553 mol, 62 kg of a 55% w/w of nitromethane in methanol) and to the stirred reaction mixture 1,8-diazabicyclo[5.4.0] undec-7-ene (0.1 equiv., 50.3 mol, 7.6 kg) was added over a period of 30 minutes under cooling, keeping the internal temperature <25° C. Stirring was continued at room temperature for 3 hours. The reaction mixture was cooled to 0° C. and sodium methoxide 2N in methanol (1.1 equiv., 553 mol, 100 kg of a 30% w/w solution of sodium methoxide in methanol) was added dropwise over 30 minutes, keeping the internal temperature at 0° C. After 30 minutes at 0° C., the reaction mixture was dosed over a period of 1 hour to a cooled (0° C.), vigorously stirred solution of concentrated sulfuric acid (2.5 equiv. 1258 mol, 128 kg of 96% sulfuric acid) in methanol (200 kg), keeping the internal temperature <10° C. The reaction mixture was further cooled to 0° C. and added to a vigorously stirred, cooled (0° C.) biphasic system of ethyl acetate (450 kg) and 1N sodium hydrogen carbonate (1.9 equiv., 1905 kg) over a period of 1 hour, keeping the internal temperature <15° C. The reaction mixture was filtered to remove most of the precipitated sodium sulfate. After phase separation, the organic phase was collected and the aqueous phase was extracted four times with ethyl acetate (total amount of ethyl acetate: 2250 kg). The collected organic phases were washed with brine (300 kg of a 23% w/w sodium chloride solution) and evaporated under reduced pressure to a residual amount of 750 kg (containing ca. 66 kg of intermediate IV.4). Intermediate IV.4 was used as such in the next step.

Synthesis of (IV.5) from (IV.4)

To a stirred solution of (IV.4) (750 kg of a solution ca. 66 kg IV.4 in methanol) was added water (38 kg) and potassium hydroxide (553 mol, 68 kg of 45% aqueous potassium hydroxide) and the reaction mixture was heated to reflux for 2 hours. After rapid cooling to 35° C., acetic acid (830 mol, 46 kg of 96% acetic acid) was added and the reaction mixture was evaporated under reduced pressure over a period of 10 hours to a residual amount of ca. 200 kg. After cooling to room temperature, more acetic acid (354 kg) was added over a period of 1 hour. After stirring for 2 hour at room temperature, most acetic acid was removed by vacuum evaporation over a period of 10 hours to a residual amount of ca. 250 kg. Water (800 kg) was added and the aqueous solution was extracted three times with ethyl acetate (3×700 kg). The combined organic layers were washed twice with 1N sodium hydrogen carbonate (2×586 kg). A third washing with 1N sodium hydrogen carbonate was performed with pH control; 1N sodium hydrogen carbonate was added until a pH of 6.8–7.2 (ca. 410 kg 1N sodium hydrogen carbonate was used). A solvent switch from ethyl acetate to isopropanol was performed by subsequent evaporation of the organic solution under reduced pressure to a residual amount of 200 kg, addition of isopropanol (350 kg), evaporation of the organic solution under reduced pressure to a residual amount of 200 kg and addition of isopropanol (350 kg). The reaction mixture was heated to 60–70° C. and isopropanol was further evaporated at that temperature under reduced pressure to a residual amount of ca. 144 kg. After filtration, the reaction mixture was cooled to 0° C. over a period of 4–5 hours, allowing crystallisation of intermediate (IV.5). Filtration and drying (vacuum drying at 40° C.) of the crystals yielded intermediate (IV.5) (27 kg). Intermediate IV.5 was used as such in the next step.

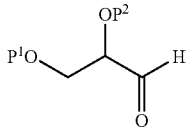
Synthesis of (7.1):

To a solution of intermediate (IV.5) (180 mol, 30 kg) in tetrahydrofuran (160 kg), lithium borohydride (1.1 equiv., 198 mol, 43.1 kg of a solution of 10% lithium borohydride in tetrahydrofuran) was added over 30 minutes. The reaction mixture was heated to 50° C. over a period of 1 hour and stirred at that temperature for 2 hours. The obtained suspension was cooled to −10° C. and hydrochloric acid (1.2 equiv. relative to $LiBH_4$, 238 mol, 27.2 kg of 32% hydrochloric acid) was dosed over a period of 4 hours, keeping the internal temperature <−5° C. After stirring at −10° C. for an additional 2 hours, triethylamine (1.1 equiv. relative to HCl, 261 mol, 26.5 kg) was added over a period of 1 hour, while maintaining the internal temperature <0° C. A solvent switch to ethyl acetate was performed by distillation of the solvents under atmospheric pressure to a residual amount of ca. 100 kg, addition of ethyl acetate (360 kg) and further distillation of the tetrahydrofuran/ethyl acetate solvent mixture with continues addition of ethyl acetate to maintain a constant volume. This procedure was continued until a tetrahydrofuran/ethyl acetate ratio of 4:1 (checked by gas chromatography). The resulting mixture was cooled to 0° C., filtered and the filter cake was washed with two portions of ethyl acetate (2×30 kg). The collected filtrates were evaporated to yield compound (7.1) (18 Kg). The identity of compound 7.1 was confirmed using HPLC, NMR and chiral gas chromatography using reference samples from Example III.

What is claimed is:

1. A method for the synthesis of hexahydro-furo[2,3-b] furan-3-ol of formula (7) starting from an intermediate of formula (1) wherein P^1 and P^2 represent each independently a hydrogen, a hydroxy-protecting group or may together form a vicinal-diol protecting group,

1



transforming said intermediate of formula (1) into a nitromethane derivative of formula (3) wherein R^1 represents alkyl, aryl or aralkyl, R^2 represents hydrogen or $C(=O)OR^3$, R^3 represents alkyl, aryl or aralkyl, or R^3, if present, and R^1 taken together with the atoms to which they are attached may form a 6 to 8-membered cyclic group which may be optionally substituted with alkyl, aralkyl, or aryl,